REMARKS

Claims 65-71 were pending in the subject application. In this amendment, Applicants have amended claim 65. Claims 65-71 are now pending in the subject application.

Claim 65 has been amended to delete the term "effective" as it relates to the term "stabilizer" and to specify that the stabilizer "inhibits degradation of one or more of the components of dalbavancin to less active or inactive materials."

Support for the amendment to claim 65 can be found in the original specification at, for example, page 26, ¶ [0091].

No new matter is added by this amendment, and Applicants respectfully request its entry.

In the Amendment filed on January 13, 2008 ("the January 13, 2008 Amendment"), Applicants argued that U.S. Patent No. 5,750,509 to Malabarba et al. ("the '509 Malabarba Patent") did not disclose any isolated form of dalbavancin having a pH of less than 7. Applicants have reconsidered the description in Example 10 of the '509 Malabarba Patent which describes a method of making dalbavancin. The last step of Example 10 of the '509 Malabarba Patent describes a purification procedure using reverse-phase chromatography on silanized silica gel in the presence of a mixture of acetonitrile and 0.1N acetic acid. Because the resin purification step described in the '509 Malabarba Patent is carried out in the presence of a mixture of acetonitrile and 0.1N acetic acid, Applicants now believe that the resultant dalbavancin API will have a pH of less than 7 and not a pH of about 7 as indicated in the January 13, 2008 Amendment. (See also Section I.C of this Amendment.) Applicants note, however, that the '509 Malabarba Patent does not disclose the exact pH of the dalbavancin isolated in Example 10, nor does the '509 Malabarba Patent disclose the amount of dalbavancin components (e.g., B_0) and non-dalbavancin components (e.g., the degradation product MAG) present in the dalbavancin isolated in Example 10. Furthermore, the '509 Malabarba Patent does not disclose a stabilizer, wherein said stabilizer inhibits degradation of one or more of the components of dalbavancin to less active or inactive materials.

The claims of the subject application are directed to stable dalbavancin pharmaceutical compositions "containing MAG in an amount of less than about 3 mole percent; at least one stabilizer, wherein said stabilizer inhibits degradation of one or more of the components of dalbavancin to less active or inactive materials; wherein the composition is lyophilized; and wherein the lyophilized pharmaceutical composition has a pH from about 3 to about 5 when reconstituted with water."

The enclosed Declaration by Paul Luner ("the Luner Declaration") at pages 2-3, paragraph 7 explains the difficulties in making lyophilized pharmaceutical compositions and notes that it

> requires consideration of numerous factors including, but not limited to: amount of API, whether the API is ionizable, whether it is an acid or a base, the counter-ion if it is a salt, the desired container physical characteristics, the glass transition temperature of the lyophile, eutectic temperature, the solubility of the API in the pre-lyophilized solution and the pH of that solution, temperature effect on solubility of the API in the solution to be lyophilized, thermal properties of the frozen solution, the tendency of the formulation to crystallize and the influence of the formulation components on crystallization, degree of supercooling in the process, achieving the desired solid content for the product after freeze drying, the physical and chemical stability of the lyophile during storage, the type and amount of liquid required to reconstitute the lyophile, the freeze drying process parameters that result in a lyophile with appropriate properties, the dissolution rate of the formulation, and residual moisture content.

The Luner Declaration further notes that making dalbavancin formulations is particularly problematic "because its solubility decreases at high pH (e.g., above pH 7) while its stability decreases at low pH" (see the Luner Declaration at page 3, paragraph 9). As further discussed in the Luner Declaration at page 3, paragraph 9, the '503 Malabarba Patent "provides no guidance or discriminatory evaluation of the components mentioned therein, to make or use a dalbavancin composition having a pH from about 3 to about 5 with a stabilizer that inhibits degradation."

For the reasons set forth below, Applicants submit that the '509 Malabarba Patent does not teach or even suggest any dalbavancin pharmaceutical composition having a pH from about 3 to about 5, let alone a lyophilized dalbavancin pharmaceutical composition which further comprises a stabilizer that "inhibits degradation of one or more of the components of dalbavancin to less active or inactive materials" as recited in amended independent claim 65.

I. Rejection of Claims 65-71 under 35 U.S.C. § 103(a)

The Examiner rejected claims 65-71 under 35 U.S.C. § 103(a) as allegedly being obvious over the '509 Malabarba Patent for the reasons set forth in the office action. In particular, the Examiner states that "Malabarba et al. disclose dalbavancin (column 3). Malabarba et al. further disclose a composition comprising dalbavancin derivative and a stabilizer (column 28, lines 9-12) and disclose said composition in the form of a powder (column 28, line 13). Malabarba et al. further disclose the combination of dalbavancin derivative in combination with a sugar, such as lactose (column 27, lines 54-56)." The Examiner contends that "[b]ased on the teaching of Malabarba et al, it would have been prima facie obvious to a person having ordinary skill in the art at the time the claimed invention was made to combine dalbavancin with a stabilizer in order to produce a more stable composition." The Examiner further contends that "the resulting pH of said composition would be expected to be around 3.01. (Note the statement in the U.S. Patent No. 7,119,061 in column 23, lines 30-34 that a dalbavancin composition which has not been pH adjusted has a pH of about 3.01)." The Examiner further states that "Malabarba et al disclose

that dalbavancin composition can be prepared in dry form in combination with a stabilizer. A dalbavancin composition in combination with a stabilizer would be expected to contain a smaller amount of a degradation product MAG than a composition in the absence of a stabilizer." Applicants traverse this rejection.

A. The '509 Malabarba Patent does not teach of suggest a composition containing a stabilizer that inhibits degradation of dalbavancin components to less active materials

As noted above, amended claim 1 of the subject application is directed to a dalbavancin composition comprising *inter alia* "at least one stabilizer, wherein said stabilizer inhibits degradation of one or more of the components of dalbavancin to less active or inactive materials." Nowhere does the '509 Malabarba Patent teach or suggest such a stabilizer. The '509 Malabarba Patent states at col. 28, lines 9-12: "Compositions for injection may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents." However, as noted in the Luner Declaration, such "formulary agents" do not encompass agents that inhibit *chemical* degradation. The Luner Declaration states at page 8, paragraph 25

> As described in the context of the '509 Malabarba Patent, I understand the term "suspending" agent to mean a component that reduces the agglomeration of particles in a dispersion to maintain a uniform suspension of solid particles in a liquid phase and increases viscosity; I understand the term "dispersing" agent to mean a component that aids or facilitates a uniform dispersion of finely divided solids in a liquid continuous phase; and I understand the term "stabilizing" agent to refer to a component useful for preventing formation of solids from a solution, preventing agglomeration of colloidal particles or maintaining the resuspendibility of coarse dispersions. Accordingly, I understand the term "formulatory agents" to refer to physical stabilizers, i.e., components whose purpose is to prevent phase separation or precipitate formation by colloids, or agglomeration of solid particles or emulsion particles in a liquid medium.

As further explained in the Luner Declaration at page 9, paragraph 26,

> the term "stability" as used in the context of the Malabarba '509 Patent is specifically, and exclusively, referring to aspects of *physical stabilization* of liquid dispersions. This is entirely different from chemical stabilization which is the object of the subject application. Also, the mechanism by which physical stabilizers function is based on different phenomena and therefore physical stabilizers used for liquid dispersion based formulations would not be useful or appropriate in providing chemical stabilization for a different type of formulation, i.e., a lyophile. (Emphasis in original.)

Thus, the '509 Malabarba Patent does not teach or suggest the use of a chemical stabilizer.

With regard to the Examiner's statement that "Malabarba et al disclose that dalbavancin composition can be prepared in dry form in combination with a stabilizer," the Luner Declaration at page 9, paragraph 27 states that the reference to "powder form for reconstitution" in the '509 Malabarba Patent at col. 28, lines 13-15 omits any mention of "formulary agents." The Luner Declaration further notes at page 9, paragraph 27 "that the omission of such 'formulatory agents' from a composition that solely consists of the 'active ingredient in powder form' indicates that that no formulatory agent (physical stabilizer) is required when the composition is in powder form."

Thus, the '509 Malabarba Patent does not provide a teaching or suggesting to use any type of stabilizing agent when the product is formulated as a powder, let alone a chemical stabilizer which inhibits degradation of one or more of the components of dalbavancin to less active or inactive materials." Therefore, even if one skilled in the art prepared a powder or lyophilized dalbavancin pharmaceutical composition containing a "formulary agent" as described in the '509 Malabarba Patent, such composition would not be expected to be stable with regard to chemical degradation of the dalbavancin components into other less active or inactive components, e.g., MAG.

The Examiner also states that "Malabarba et al. further disclose the combination of dalbavancin derivative in combination with a sugar, such as lactose (column 27, lines 54-56)." However, the Examiner's reliance on this description in the '509 Malabarba Patent is a misunderstanding of the teachings of the '509 Malabarba Patent. As explained in the Luner Declaration at page 9, paragraph 28, "the reference to 'lactose' in the '509 Malabarba Patent is as a 'diluent' for a 'tablet' as stated at col. 27, line 54-55 [of the '509 Malabarba Patent]. The use of lactose as a diluent for an oral formulation such as a tablet is a completely separate endeavor from the use of a lactose as a stabilizer in a lyophilized dalbavancin pharmaceutical formulation that will be reconstituted and administered by injection or infusion." Thus, the reference to a tablet formulation containing lactose would provide no guidance or suggestion to one skilled in the art to use lactose in a lyophilized formulation that is suitable for injection or infusion.

In summary, the '509 Malabarba Patent does not teach or suggest a lyophilized dalbavancin composition comprising "a stabilizer that inhibits degradation of one or more of the components of dalbavancin to less active or inactive materials." Moreover, nowhere does the '509 Malabarba Patent teach or suggest that dalbavancin should be stabilized against degradation of the dalbavancin components "into one or more of the components of dalbavancin" such as, e.g., MAG.

"Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so." MPEP § 2143.01.I (citing *In re Kahn*, 441 F.3d 977, 986 (Fed. Cir. 2006)).

For the reasons discussed above, the '509 Malabarba Patent only describes the use physical stabilizers in its liquid-containing formulations. However, the '509 Malabarba Patent does not describe the use of chemical stabilizers in any formulation. Moreover, the '509 Malabarba Patent does not teach or suggest that chemical degradation of dalbavancin should be inhibited. Thus, one of ordinary skill in the art would find no teaching, suggestion, or motivation in the '509 Malabarba Patent to make or use a dalbavancin formulation containing a chemical stabilizer, i.e., "a stabilizer that inhibits degradation of one or more of the components of dalbavancin to less active or inactive materials" as recited in amended claim 65 of the subject application. Therefore, amended claim 65 is not obvious over the '509 Malabarba Patent for at least this reason.

B. The '509 Malabarba Patent does not disclose or suggest a stabilized dalbavancin composition having a pH of from about 3 to about 5

As noted in the Luner Declaration at page 2, paragraph 7, "the '509 Malabarba Patent is concerned with the preparation of compounds or Active Pharmaceutical Ingredients ("APIs"), not pharmaceutical formulations; it only refers to formulating APIs as pharmaceutical formulations in a non-specific and very general manner." Moreover, nothing in the '509 Malabarba Patent teaches or suggests making or using acidic dalbavancin pharmaceutical formulations, e.g., having a pH of from about 3 to about 5. The Luner Declaration at page 3, paragraph 10 to page 6, paragraph 16, explains the stability data described in U.S. Patent No. 7,119,061 to Stogniew et al. ("the '061 Stogniew Patent") at col. 22, line 54 to col. 31, line 54 and notes that lyophilized dalbavancin compositions become less stable at lower pH; however, the Luner Declaration states that such instability can be inhibited by use of "a stabilizer that inhibits degradation of one or more of the components of dalbavancin to less active or inactive materials" (i.e, a chemical stabilizer).

For the reasons discussed in Section I.A above, the '509 Malabarba Patent does not teach or suggest using a chemical stabilizer in any dalbavancin formulation. Thus, even if the '509 Malabarba Patent discloses dalbavancin having a pH of about 3.01 as posited by the Examiner, the Luner Declaration at page 6, paragraph 17 states that "a lyophilized composition containing such form of 'dalbavancin with no other non-dalbavancin components and which has not been pH adjusted' [would be expected] to contain about 4.5 mol % MAG." This amount of MAG (4.5 mol %) is greater than the 3 mole percent or less recited in claim 65 of the subject application. Thus, claim 65 is not obvious over the '509 Malabarba Patent for at least this reason, too.

C. Requirement to clarify the pH of dalbavancin in the '509 Malabarba Patent

The Examiner further states "[w]ith respect to the composition disclosed by Malabarba et al. applicant has not made of record any evidence in verified form showing the pH of the

composition disclosed by Malabarba et al. Further, applicant has not explained the statement in the U.S. Patent No. 7,119,061 that dalbavancin composition which has a pH of about 3.01 has not been pH adjusted." Applicants first note that the Examiner's reference to the '061 Stogniew Patent is for information purposes only, because the '061 Stogniew Patent is a family member of the subject application. As explained in the Luner Declaration at page 6, paragraph 16

> I understand the statement in the '061 Stogniew Patent that Composition D "has not been pH adjusted" to mean that a 10 ml solution composed of 250 mg dalbavancin API (prepared and isolated according to Example 11 of the '061 Stogniew Patent) and water had a pH of 3.01; the solution was then lyophilized without any further adjustment of pH. The statement does not refer to pH adjustments that may have been carried out during the preparation and isolation of the dalbavancin API (such as those described in Example 11 of the '061 Stogniew Patent).

As noted by the Luner Declaration, Composition D in the '061 Stogniew Patent was prepared using dalbavancin API where the pH adjustment step was carried out during preparation of the dalbavancin API (according to Example 11) and not during lyophilization or the preparation of the pre-lyophilate. Applicants believe that the above-cited section of the Luner Declaration fully addresses the Examiner's requirement with regard to the statement in the '061 Stogniew Patent that Composition D "has not been pH adjusted."

With regard to the requirement to show the pH of the dalbavancin disclosed by the '509 Malabarba Patent in a verified form, Applicants note that the Luner Declaration states at page 6, paragraph 17 that

> A method of making dalbavancin API is disclosed in the '509 Malabarba Patent in Example 10, col. 32, lines 20 to 38, and a method of purifying dalbavancin API using reverse-phase chromatography on silanized silica gel is disclosed in the '509 Malabarba Patent at col. 34, lines 39-61. Because the resin purification step described in the '509 Malabarba Patent is carried out in the presence of a mixture of acetonitrile and 0.1N acetic acid, I believe that the resultant dalbavancin API will have a pH of less than 7. In other words, dissolving 250 mg of dalbavancin API from Example 10 of the '509 Malabarba Patent in 10 ml of water (as described in the '061 Stogniew Patent at col. 20, lines 47-50 and Table 4) would produce an aqueous solution having a pH of less than 7. However, the '509 Malabarba Patent does not disclose the exact pH or the MAG content of its dalbavancin.

Thus, the pH of the dalbavancin isolated according to Example 10 of the '509 Malabarba Patent will likely by less than 7 but the exact pH is not reported in the '509 Malabarba Patent. Applicants believe that the above-cited section of the Luner Declaration fully addresses the

Examiner's requirement to show the pH of the composition disclosed by the '509 Malabarba Patent in verified form.

In summary, Applicants respectfully submit that one of skill in the art would find no suggestion or motivation in the '509 Malabarba Patent to make or use a lyophilized dalbavancin composition having a pH from about 3 to about 5 and containing "a stabilizer that inhibits degradation of one or more of the components of dalbavancin to less active or inactive materials" as recited in amended claim 65 of the subject application. Accordingly, claims 65 and claims 66-71 which depend directly or indirectly upon claim 65 are not obvious over the '509 Malabarba Patent.

In view of the above, Applicants submit that claims 65-71 are not obvious over the '509 Malabarba Patent, and request that the rejection of claims 65-71 under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

Applicants respectfully request prompt consideration of the pending claims and early allowance of the application. No additional fee is believed due. However, if any fee is due, the Examiner is authorized to charge the fee to Applicants' Deposit Account No. 16-1445.

If the Examiner wishes to comment or discuss any aspect of this application or response, Applicants' undersigned attorney invites the Examiner to call him at the telephone number provided below.

Respectfully submitted,

Date: June 10, 2008

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Enclosures

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